

REMARKS/ARGUMENTS

Claims 1 to 23, 25 to 54 and 69 are pending in the application. Claims 1 and 69 have been amended, without prejudice. Elements of dependent claim 24, which has been canceled, have been incorporated into independent claims 1 and 69. Claims 55 to 62, which were indicated as being allowable, have been canceled, without prejudice. Claims 63 to 68 and 70 to 72, which stood rejected under 35 U.S.C. §§ 102 and/or 103, have been canceled, without prejudice. Applicants respectfully disagree with the rejections set forth in the Office Action, but have cancelled the rejected claims to advance prosecution of the instant application to allowance. Applicants expressly reserve the right to file one or more continuing applications directed to any deleted subject matter.

Also submitted herewith is a Supplemental Information Disclosure Statement (SIDS), that contains all of the art that Applicants are aware of that may have potential relevance to this application. It is believed that virtually all of the references cited in the attached SIDS will likely have already been considered by the Examiner, as these references have also been cited in numerous other applications that have been in front of this Examiner. Attention is directed in particular, however, to item 497, Schneider et al., U.S. Patent No. 6,258,378 ("Schneider"), and its file history.

Schneider teaches compositions that contain both liquid filled liposomes and gas filled microspheres, such as "microbubbles." *See* abstract. Schneider further teaches that the gas filled microspheres may simply be admixed with liposome vesicles, or the gas-filled microspheres and liposomes may each be provided with the molecular components of a conjugate pair, so that they are coupled to each other. *See* col. 5, lines 45 to 56. In a response submitted during prosecution of Schneider, certain diagrams were attached that

apparently reflect Schneider's interpretation of the compositions described in that patent (*see* Amendment After Final Rejection of U.S. Application Serial No. 09/243,787 filed March 9, 2001). Without conceding that these diagrams in any way accurately reflect the compositions that one of ordinary skill in the art would understand to be taught by the Schneider patent, or that the file history of the Schneider patent is prior art to the instant application, Applicants wish, in the interest of full disclosure, to bring both the Schneider patent, and the proprietor's interpretation of same, to the Examiner's attention.

Applicants respectfully submit that despite any arguable similarity between the Schneider diagrams and the figures of the instant application, Schneider does not teach or suggest the gas microsphere liposome composites as defined by Applicants' claims. In particular, Applicants note that claim 1 has been amended to specify that the liquid-filled liposomes used in the composites of the present invention each have a diameter of about 20nm to about 100nm. Applicants submit that Schneider completely fails to teach or suggest composite structures in which the liquid filled liposomes are within the claimed size range. In this regard it is noted that Schneider describes liposomes having an average diameter in a range of from about 1.3 μm (*see* Example 1, col. 9, line 45), which would be more than 10 times the size of the largest liposomes of the present invention, down to 260 nm (*see* Example 3, col. 11, Table 3), which is still more than 2.5 times the size of the largest liposomes of the present invention. Thus, Schneider does not teach or suggest liposome composites that contain liposomes in the size range defined in the amended claims.

Moreover, Schneider completely fails to provide any motivation or expectation of success that would lead one of ordinary skill in the art to the composites of the present invention. In particular, Schneider shows in Example 3 that the use of liposome vesicles at


DOCKET NO.: PH-7103 (BMS-0698)
Application No.: 09/931,317
Office Action Dated: February 5, 2003

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the smaller end of the described size range (but still outside the size range in Applicants' claims) led to an undesirable reduction in both the ratio of encapsulation and percentage release of the therapeutic compound from the liposomes upon application of ultrasound (*see id.*). Thus, Schneider may be said to *teach away* from the use of liposomes that fall within the smaller end of size range disclosed in that patent. On the basis of this teaching, one of skill in the art would not be motivated to prepare composites that comprise liquid filled liposomes that are even smaller than the ones described in Schneider. Nor would the skilled artisan have a reasonable expectation that such a modification would succeed. Accordingly, Applicants respectfully submit that present claims clearly define over Schneider, under both Sections 102 and 103

Having established that Schneider does not impact the patentability of the pending claims, and there being no further rejections pending in this application, a Notice of Allowance of pending Claims 1 to 23, 25 to 54 and 69 is respectfully requested.

Date: June 30, 2003


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